and its increasingly sophisticated successors has made consideration of centrosymmetricity essentially a non-issue in structure solution and refinement.

Nevertheless, the question of the relationship between molecular symmetry and crystallographic symmetry remains one of considerable importance, especially with regard to crystal engineering and the interest in engineering non-centrosymmetric crystals, for instance for the generation crystals exhibiting non-linear optical effects.

Kitaigorodskii [1] claimed that centrosymmetric molecules essentially universally crystallize in centrosymmetric space groups. However, many molecules lacking a center of symmetry also tend to crystallize in centrosymmetric space groups, e.g. $P2_1/c$, P1-bar, C2/c, etc. While chiral molecules must crystallize in chiral space groups, it is not clear why some achiral molecules also do so. In the case of polymorphic systems some members may be centrosymmetric and others non-centrosymmetric, providing clues as to how one might achieve a desired either one of the situations.

This presentation will include a number of examples from our own work, in addition to some possible strategies for the generation of centrosymmetric or non-centrosymmetric structures.

[1] Kitaigorodskii A.I., *Organic Chemical Crystallography*, Consultants Bureau, New York, 1961.

Keywords: polymorphism, polar crystal, crystallization conditions

MS04 POLYMORPHISM

Chairpersons: Shiv P. Halasyamani, Reiko Kuroda

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Modifying Nucleation Kinetics of Polymorphic Crystals in Bulk and Emulsion States

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This paper discusses thermodynamic and kinetic influences on nucleation processes of polymorphic crystalline systems in bulk and emulsion states in comparative ways. Three main characteristics may be revealed in the crystallization processes in emulsion droplets: (1) reduction in nucleation rate caused by thermodynamic and kinetic effects, (2) interfacial crystallization caused by molecular interactions between interfacial membrane and the solute molecules, and (3) droplet-droplet interactions of two kinds; dilution of solute/solvent molecules which are slightly soluble in the continuous phase, and partial coalescence of the particles after crystallization. Based on recent experimental work of melt crystallization of long-chain lipophilic materials in oil-in-water emulsion droplets, we discuss the polymorphic crystallization behavior related to the reduction in nucleation rate and the interfacial crystallization.

Keywords: polymorphism, nucleation kinetics, emulsion

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Controlling Crystal Polymorphism: from Stability Prediction to Crystallization Process Design

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Investigations of crystal polymorphism are usually conducted early in drug development to optimize the physical properties of a pharmaceutical solid. Although the thermodynamically most stable crystal form is generally selected for a drug product, controlling polymorph appearance must be accomplished through careful evaluation of both thermodynamic (tendency toward the formation of more stable polymorphs) and kinetic parameters (which lead to the formation of metastable polymorphs) in the crystallization process. The first step in designing a crystallization process should be to evaluate the thermodynamic stability relationship(s) (monotropy or enantiotropy), i.e., free energy differences (ΔG), between the polymorphs as a function of temperature. A number of tools (including, but not limited to, DSC analysis of pure and eutectic melting, solubility, intrinsic dissolution, solution calorimetry and slurry bridging) can be used collectively to assess ΔG over a wide range of temperatures. While qualitative approaches, which yield the sign of ΔG only, are useful for assessing the risk of unwanted phase transformations, quantitative studies allow for the thermodynamic transition temperature of enantiotropic polymorph pairs and differences in important physical properties (solubility, intrinsic dissolution rate) to be predicted. A number of factors, including structural similarities between crystal polymorphs, comparable thermodynamic stability, ease of crystal nucleation, and overlap of occurrence domains (metastable zones), have been shown to contribute to poor polymorph selectivity during crystallization. All of these factors must be considered in implementing strategies to control polymorph appearance.

Keywords: polymorph, crystallization, stability

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Crystal Structure Prediction: Theory, Applications and Challenges

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Although crystal structure prediction from first principles is now less controversial and more mainstream than when the first applications were reported in the early 1990's, it is debatable whether it is possible to reliably predict the observable polymorphs of simple organic molecules.

In this contribution, the theory of crystal structure prediction will be reviewed and illustrated with recent application examples (e.g., [1, 2]), including the three so-called 'blind tests' organised by the Cambridge Crystallographic Data Centre [3].

Despite significant progress since the early 1990's, many challenges still remain, such as the treatment of flexible molecules and the accurate description of polymorphic stability [4]. Related areas of research that merit particular attention are the simulation of crystal nucleation and the consideration of kinetics in crystal growth simulations [5]. The latest research aims to address the fundamental question why certain polymorphs crystallise and grow, whereas other structures, which are predicted to be thermodynamically stable, cannot be obtained experimentally.

[1] Leusen F.J.J., *Crystal Growth & Design*, 2003, **3**, 189–192. [2] Price S.L., *Advanced Drug Delivery Reviews*, 2004, **56**, 301–319. [3] Motherwell W.D.S., et al., *Acta Crystallographica B*, 2002, **58**, 64 –661. [4] Brodersen S., Wilke S., Leusen F.J.J., Engel G.E., *Physical Chemistry Chemical Physics*, 2003, **5**, 4923–4931. [5] Bennema P., et al., *Crystal Growth & Design*, 2004, **4**, 905-913.

Keywords: polymorphism, crystal modelling, molecular mechanics

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Polymorphism in Co-Crystals and Pharmaceutical Co-Crystals

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Pharmaceuticals are perhaps the most valuable materials known to mankind and there are important intellectual property, regulatory and efficacy implications if one is able to discover new compositions of matter for active pharmaceutical ingredients (API's). Emphasis will be placed on pharmaceutical co-crystals,[1] a long known but little explored alternative to the three accepted forms of API (polymorphs, solvates, salts).

The presentation will detail how one can exploit the principles of crystal engineering to design and generate novel pharmaceutical co-crystal phases that contain one or more API's. Examples to be presented will include well-known API's such as aspirin, ibuprofen, carbamazepine and piracetam. CSD surveys and structural and physical studies on new co-crystals will be presented in order to address the relative stability of pharmaceutical co-crystal phases with